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Closing PFO closure for migraine?

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This editorial refers to 'Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial', by H.P. Mattle *et al.*, on page 2029.

Mattle and co-workers present PRIMA, a randomized clinical trial comparing patent foramen ovale (PFO) closure using the Amplatzer occluder with medical management in patients suffering from migraine with aura (MA).[1] The primary endpoint—the reduction in monthly migraine days between months 9 and 12 after randomization and 3 months before randomization—was not reached. Numerically, patients after PFO closure had a 1.2 day greater reduction in migraine days per month than controls, but this difference was not statistically significant. A secondary endpoint—response to therapy as defined by a reduction ≥50% of migraine days per month—was significant (38% of PFO closure patients vs. 15% of controls). Serious adverse events (SAE) occurred in 13% of closure patients and were procedure related in 11%; no SAE had lasting con- sequences. The PRIMA trial was terminated early due to slow enrolment. Of the 53 patients that were randomized to PFO closure, only 45 finally agreed to the procedure, the device was implanted in 41 (77%), and successful closure was adjudicated at 6 months in 35 (66%). This may have obscured a possible benefit in the intention-to-treat analysis. On the other hand, interventions in migraine treatment carry a substantial placebo effect with respect to the reduction in migraine frequency.[2] Intervention-related placebo effects were not controlled in PRIMA because medical treatment instead of a sham procedure was used as comparison. The placebo effect may have contributed to beneficial effects of PFO closure. Regardless of these limitations, the PRIMA results are consistent with those of the MIST trial which failed to demonstrate that PFO closure produced more frequent cessation of headache than a sham intervention.[3]

Is PFO closure in MA patients now proven to be ineffective? This conclusion cannot be drawn from the trial data available to date. While these data preclude the use of PFO closure as a routine procedure outside of clinical trials, the scientific arguments for investigating the PFO closure approach to migraine prophylaxis remain valid and demand further research. One argument is the epidemiological link between MA and PFO which has been demonstrated in migrainers showing a higher frequency of PFOs, and vice versa.[4] More importantly, microemboli that reach the brain through a right-to-left shunt may produce aura attacks by inducing cortical spreading depression (CSD).[5] CSD consists of waves of neuronal and glial depolarization that propagate slowly across the cortex and are followed by hyper- and hypoperfusion. CSD is one mechanism proposed to cause migraine aura.[6] CSDs also occur after stroke, subarachnoid haemorrhage, and brain injury.[7] Microemboli may cause CSD in a brain that is susceptible. Genetically de- fined susceptibility is evident in CADASIL, the cerebral autosomal dominant angiopathy with subcortical infarcts and leukencephalopathy, where a mutation in the Notch-3 gene leads to dysfunctional vascular smooth muscle

cells resulting in deficient autoregulation of cerebral arteries and arterioles.[8] Endothelial dysfunction may be another reason for CSD susceptibility.[5] Epidemiological links exist between migraine and conditions associated with endothelial cell dysfunction such as Raynaud's phenomenon,[9] Moyamoya disease,[10] vascular retinopathy,[11] and Sjogren's syndrome.[12] Von Willebrand factor level, a marker of endothelial cell dysfunction, is increased in[13] and between migraine attacks.[14] In addition, platelets may be dysfunctional in migraine patients.[15] Taken together, these conditions predispose the MA patient to focal brain ischaemia which can trigger CSD and in turn cause aura and headaches (*Figure 1*).

Based on the pathophysiology, it is plausible that an aura can be induced by a paradoxical embolus travelling through a PFO. This induction is a probabilistic event. Not every embolus will produce an attack nor will every attack be caused by an embolus in the patient with MA and a PFO because CSD can be triggered by a variety of events. The probabilistic link will decrease effect size and require larger sample sizes to prove the efficacy of PFO closure in MA. Considering additional uncertainty in clinical trials provided by patient-related and methodological factors, as evident in the intention-to-treat analysis of PRIMA, a proof of efficacy will require careful patient selection. How to select patients is an open question. Taking the extreme view, PFO closure may only be a valuable treatment option for those who have a migraine attack triggered by a bubble test, i.e. the intravenous injection of agitated saline giving rise to air microemboli that travel through the PFO to produce transient brain ischaemia and CSD.[16] Electroencephalography or functional magnetic resonance imaging could provide surrogate markers to identify clinically silent CSD and be used to widen patient selection.

It seems reasonable to select patients with large PFOs and right-to-left shunt at rest who have a higher likelihood for microemboli. In light of PRIMA that was terminated due to slow recruitment, it seems unlikely that a future trial will be able to recruit a sufficiently large sample of selected patients. However, before giving up a potentially beneficial strategy to help migraine sufferers, cardiologists and neurologists need to join forces to obtain the scientific evidence that is currently lacking.

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